

REMARKS

Claim 20 is currently pending in the application. Applicants herein add new claims 21 and 22 to more clearly set forth the invention or to correct a typographical error (deletion of extraneous "from" in claim 20). No new matter has been added. Claim 20 is the only claim in independent form.

Applicants wish to express their appreciation for the courtesies extended Applicants' representative, Laura S. Dellal, during a personal interview conducted on June 11, 2009. During the interview, the amendments to the claims herein were discussed that more clearly define the claims over the cited prior art. The Declaration of Applicant Dr. Michael Tainsky was also discussed in support of the amendments and arguments herein.

Claim 20 stands rejected under 35 U.S.C. §103(b) as being unpatentable over Sioud, *et al.* in view of WO 99/39210 to Miller, *et al.* The Office Action holds that Sioud, *et al.* teaches the analysis of the humoral response in patients with cancer; but does not specifically teach a "microarray of markers within sera". The Office Action further holds that Miller, *et al.* teaches a high-density protein array for proteome analysis and that it would therefore have been *prima facie* obvious to one skilled in the art to have utilized the techniques of Sioud, *et al.* to biopan and select clones to array in a large format as presented by Miller, *et al.*

Claim 20 also stands rejected under 35 U.S.C. §103(b) as being unpatentable over Sioud, *et al.* in view of U.S. Patent Application Publication No. 2003/0003516 to Robinson, *et al.* The Office Action holds that Sioud, *et al.* does not specifically teach a microarray of markers within sera. The Office Action further holds that Robinson, *et al.* teach epitope arrays, including high density arrays, for determining an antibody specificity profile in a patient; and that it would have been *prima facie* obvious to one skilled in the art to have utilized the techniques of Sioud,

et al. to biopan and select clones to array in the high density array of Robinson, *et al.*

In response thereto, the claims have been amended to point out and distinctly claim two bioinformatic elements of the array methods of the present invention which are neither known in the art nor disclosed nor suggested by any of the cited references.

"Any need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed"; however, that reason must be present for the combination to be obvious. *KSR Intern Co. v. Teleflex*, 127 S. Ct. 1727, 1742, U.S. (2007). This requirement was confirmed in *Takeda Chem. Indust., et al. v. Alphapharm*, No. 06-1329 (Fed. Cir. 2007).

"The key to supporting any rejection under 35 U.S.C. 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious. The Supreme Court in *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385, 1396 (2007) noted that the analysis supporting a rejection under 35 U.S.C. 103 should be made explicit." MPEP Section 2143.

"The rationale to support a conclusion that the claim would have been obvious is that all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination yielded nothing more than predictable results to one of ordinary skill in the art." *KSR International Co. v. Teleflex Inc.*, 83 UDPQ2d 1385, 1395 (2007) and MPEP Section 2143.

Applicants submit herein the Declaration of Dr. Michael Tainsky, an inventor of the present invention.

The present invention includes at least two novel solutions to problems that the applicants have found to be important impediments to assembling high density panels of tumor markers that are both accurate in diagnosing cancer yet compact enough to be technically and economically feasible.

The first problem is the occurrence of control sera with high but nonspecific activity to certain epitopes. This phenomenon causes the erroneous rejection of epitopes which are potentially useful tumor markers, because epitopes reactive with control serum are excluded from marker panels constructed through phage display. (paragraph 0088, lines 4-17).

The solution to this problem is the step of recognizing and excluding the sera of normal individuals that react strongly but nonspecifically to epitope bearing clones. This step has now been incorporated into amended claim 20. The amendment is supported by a specific embodiment of the solution, which is fully described in the specification and is itself the subject of new dependent claim 21: the step of excluding sera which show a unimodal pattern of dual fluorescence reaction with epitope bearing clones, where a first color indicates reaction with human Ig and a second color indicates reaction to phage capsid proteins.

Essentially, this step requires that, if a phage clone stains positively for binding of human Ig of a control serum, but the staining is not sufficiently intense to form a fluorescence peak separate from that produced by immunofluorescence staining of phage capsid protein (i.e. unimodal dual fluorescence distribution, as in Figs. 8A and 9A), then that phage clone is not discarded as bearing an epitope reactive with an Ig of a normal individual. Instead, the serum is excluded from the analysis, for the unimodal fluorescence marks it as containing Ig's which bind nonspecifically to the phage clone. Phage clones are discarded only when the binding of human Ig of a control serum produces fluorescence which surpasses the immunofluorescence staining of phage capsid proteins sufficiently to produce a separate peak on a logarithmic scale (i.e. bimodal dual fluorescence distribution, as in Figs 8B and 9B).

The amendment is supported in the disclosure in paragraph 0088. There the problem is recognized and the solution is explained, including references to

Figs 8 and 9, which show the distinction between unimodal and bimodal fluorescence profiles. The construction of the histograms for determination of unimodal vs. bimodal fluorescence distribution is further explained in paragraphs 0165-0166. The unimodal vs. bimodal fluorescence analysis is used to reduce the artifactual elimination of potentially useful tumor markers in Example 1, in paragraph 0159. That is part of the analysis of epitope expression in a phage display library constructed from ovarian tumor cells.

It must be stressed that the step of recognizing and excluding the sera of normal individuals which react strongly but nonspecifically to epitope bearing clones is not a normalization step, but a step performed after normalization is complete. Normalization is provided as the part of the first major step of data analysis, "Pre processing and normalization" (Paragraphs 0077 and 0078). The purpose of normalization, explained in paragraph 0081, is to cleanse the data of artifacts such as slide contamination, differential dye incorporation, scanning and image processing problems, and imperfect spots due to imperfect arraying, washing, drying, etc. The techniques of normalization are described in paragraph 0082. In contrast, the step of recognizing and excluding the sera of normal individuals which react strongly but nonspecifically to epitope bearing clones is performed as part of the second major step of data analysis, "Identifying the most informative markers" (Paragraph 0079).

Neither Sioud, *et al.* nor Miller, *et al.*, nor Robinson, *et al.* disclose all of the limitations of the presently amended independent claim 20 and new dependent claim 21. Sioud, *et al.* teaches densitometric comparisons of phage clones with cancer patient Ig and control Ig (page 717, last paragraph, to page 718, first paragraph). . There is no recognition of the possibility of artifactual exclusion of useful epitopes because of intense but nonspecific binding of control Ig to phage, and no solution to the problem is disclosed. Miller, *et al.* teaches only normalization of the same type disclosed as the normalization step of the present invention. Reporter molecules are used to correct for variations in the amount of

protein spotted on a solid support (page 48 lines 21-29), or to correct for variations in the amount of antibody spotted on a solid support or for variations in the association and dissociation constants of different antibodies to the same protein (page 52 line 21 to page 53 line 8). There is no recognition of the possibility of erroneous exclusion of useful epitopes because of intense but nonspecific binding of control Ig to a possible marker, and no solution to the problem is disclosed or suggested. Robinson, *et al.* discloses methods of two color staining of arrays in paragraphs 0070 to 0077, with paragraph 0074 focusing especially on the use of negative and positive controls. Again, there is no recognition of the possibility of erroneous exclusion of useful epitopes because of intense but nonspecific binding of control Ig to a possible marker, and no solution to the problem is disclosed or suggested.

In summary, the cited references, alone or in combination with knowledge in the art, disclose neither the general concept of recognizing and excluding the sera of normal individuals which react strongly but nonspecifically to epitope bearing clones, nor the specific embodiment of excluding sera which show a unimodal pattern of dual fluorescence reaction with epitope bearing clones. No combination of references protects against the unnecessary elimination of useful epitopes as does the present invention. Consequently, it is respectfully submitted that amended claim 20 and new claim 21 are clearly patentable over the combinations of Sioud, *et al.* with either Miller, *et al.*, or Robinson, *et al.* Reconsideration of the rejection is respectfully requested.

The second problem recognized by the applicants and solved by the invention is the problem of patient sera which react to only a small number of very specific epitopes. If the selection of the epitopes is done on statistical grounds alone, these very specific epitopes can be missed. Simply including all such epitopes, however, can result in panels of unacceptable size. This problem is an obstacle to the assembly of a high density panel of tumor markers that is

both accurate in its ability to diagnose cancer yet compact enough to be technically and economically feasible.

The solution to this problem is to maximize the information content of the selected panel of markers while minimizing the number of epitopes included. This solution is now incorporated into amended claim 20. The amendment is supported by a description of the problem and solution paragraph 0089. Note that the solution is referred to therein as an "essential modification" to the procedure of identifying the most informative markers.

A specific embodiment of this solution is the subject of new dependent claim 22. It is a method enforcing the following condition: epitopes that are solely self reactive – that is epitopes that react only with the serum of the patient used to isolate the epitope – are included in the panel only if that self serum does NOT also cross react with epitopes isolated with sera of other patients. If the self serum DOES cross react with epitopes isolated with other sera, the solely self reactive epitope can be excluded. This method permits the user to exclude some solely self reactive epitopes while ensuring that the resulting array retains information from all patient sera in the sample (paragraph 0096, last line). Claim 22 is supported in paragraphs 0093-0096, which teach the making of epitope inclusion decisions through the construction and progressive editing of a table of reactive clones and patient sera. The method is also described in Example 1, in paragraph 0164.

None of the cited references recognizes the problem of ensuring the inclusion of rare but informative epitopes while minimizing the number of epitopes included in the panel of markers, and none of them provide or suggest any solution. Sioud, et al. does not treat the problem as it does not disclose a high density array. Neither of the two references which provide high density arrays, i.e Miller, *et al.*, and Robinson, *et al.* contemplate any practical limits on the size of marker panels resulting from their arrays, nor of the possible need to limit the inclusion of rare but possibly informative markers. Consequently, it is

respectfully submitted that amended claim 20 and new claim 22 are clearly patentable over the combinations of Sioud, *et al.* with either Miller, *et al.*, or Robinson, *et al.* Reconsideration of the rejection is respectfully requested.

There is an additional reason why the present invention is not rendered obvious by Sioud, *et al.* in view of Miller, *et al.* Miller, *et al.* teaches the creation of an array of defined monoclonal antibodies with which to detect differences in protein expression among samples of tissue and body fluid. The present invention creates an array of defined proteins or peptides with which to detect differences in anti-tumor antibody expression in body fluids of normal individuals and cancer patients. This inventive concept exactly opposes the teaching of Miller, *et al.* The inventive concept of Sioud, *et al.* also exactly opposes the teachings of Miller, *et al.* It entails the definition of individual proteins with which to detect differences in anti-tumor antibody expression in body fluids of normal individuals and cancer patients. The antibody-based detection method taught by Miller, *et al.* therefore cannot be combined with the protein based detection method taught by Sioud, *et al.* in any useful way.

Since neither the cited references alone or in combination with knowledge in the art suggest the currently claimed invention, it is consequently respectfully submitted that the claims are clearly patentable over the combination, even if the combination were to be applied in opposition to applicable law, and reconsideration of the rejection is respectfully requested.

There is an additional reason why the present invention is not rendered obvious by Sioud, *et al.* in view of Robinson, *et al.* The array disclosed by Robinson *et al.* is essentially an ELISA plate assay. The combination of this array with the phage display methods taught by Sioud, *et al.* would produce methods which would not be feasible, in terms of time and cost, for the screening of candidate marker populations of the size which can be screened by the present invention.

Since neither the cited references alone or in combination with knowledge in the art suggest the currently claimed invention, it is consequently respectfully submitted that the claims are clearly patentable over the combination, even if the combination were to be applied in opposition to applicable law, and reconsideration of the rejection is respectfully requested.

In view of the present amendment and foregoing remarks, reconsideration of the rejections and advancement of the case to issue are respectfully requested. If any remaining issues exist, applicants request to be contacted by telephone at (248) 539-5050.

The Commissioner is authorized to charge any fee or credit any overpayment in connection with this communication to our Deposit Account No. 11-1449.

Respectfully submitted,

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Dated: December 15, 2009

CERTIFICATE OF ELECTRONIC FILING VIA EFS-WEB

Date of Electronic Filing: December 15, 2009

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